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EXAMINER	
REDDIG, PETER J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,224	MUELLER-HERMELINK ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/29/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-116, 120-130, 133 and 134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *133 and 134* is/are allowed.

6)☒ Claim(s) *111-116,120-122 and 124-130* is/are rejected.

7)☒ Claim(s) *123* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed December 29, 2009 in response to the Office Action of July 31, 2009 is acknowledged and has been entered. Claim 112 has been amended. Claims 111-116, 120-130, 133 and 134 are currently being examined.

Oath/Declaration

2. The Declaration of Dr. Vollmers under 37 CFR 1.132 filed December 29, 2009 is sufficient to overcome the rejection of claims 111-116, 120-130, 133 and 134 based upon their rejection under USC 112, first paragraph as lacking an adequate written description.

3. The Declaration of Dr. Vollmers under 37 CFR 1.132 filed December 29, 2009 is insufficient to overcome the rejection of claim 111-116, 120-130, 133 and 134 based upon their rejection under 35 U.S.C. 112, first paragraph, set forth in section 11 of the Office Action of 07/30/2009 as failing to comply with the enablement requirement as set forth in the last Office action because the totality of the evidence does not provide enablement of the claims for the reasons set forth below.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 111-116, 120-122, and 124-130 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in section 7 of the Office action of July 30, 2009, which are set forth below.

. . .because the specification, while being enabling for a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein said antibody or antigen binding fragment thereof binds to the epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell specifically bound by the PM-2 antibody produced by a cell line deposited as DSM ACC2600, *does not* reasonably provide enablement for a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell, wherein said antibody binds the carcinomas of claim 126, inhibits proliferation of adenocarcinoma cells of the pancreas in vitro, or inhibits proliferation or induces apoptosis of BXPC-3 cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell, wherein said antibody binds the carcinomas of claim 126, inhibits proliferation of adenocarcinoma cells of the pancreas in vitro, or inhibits proliferation or induces apoptosis of BXPC-3 cells. Thus, the claims encompass, given the indefinite nature of the "said epitope" in the wherein clause and given their broadest reasonable interpretation, antibodies that bind to a polypeptide or an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl

sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells that are distinct from the epitope or polypeptide bound by the PM-2 antibody produced by a cell line deposited as DSM ACC22600. The claims also encompass antibodies or antigen binding fragments comprising sequences with varying identity to SEQ ID NO: 5 and/or 7 that bind this genus of epitopes and proteins. Thus, the claims encompass a genus of antibodies binding to unknown epitopes on unknown proteins.

The specification teaches that SEQ ID NO: 5 and SEQ ID NO: 7 are the amino acid sequences of the variable regions of the light and heavy chains of monoclonal antibody PM-2, see Figure 14 and 15. The specification teaches that the PM-2 monoclonal antibody expressing hybridoma cell line was generated from lymphocytes from pancreatic cancer patients fused to heteromyeloma cell lines. The specification teaches that CDR1 of the PM-2 variable region light chain spans nucleotides 76-102 which encode amino acids 26-34, CDR2 spans nucleotides 154-1 74 which encode amino acids 52-58, and CDR3 spans nucleotides 289-309, which encode amino acids 97- 103. The specification teaches that CDR1 of the PM-2 variable region heavy chain spans nucleotides 3 1-54 which encode amino acids 11-18, CDR2 spans nucleotides 106-129 which encode amino acids 36-43, and CDR3 spans nucleotides 244-300, which encode amino acids 82-100, see Example 2.

The specification teaches that the PM-2 antibody does not stain any normal tissue in immunohistochemical assays, while it positively stains every tumor type tested, see Example 3 and Tables 3 and 4. The specification teaches that The PM-2 antibody specifically binds to the CACO-2 human colorectal adenocarcinoma cell line (ATCC Accession No. HBT-37, DSMZ Accession No. ACC 169), the human colon carcinoma cell line COLO-320 (DSMZ Accession No. ACC 144), the human colon carcinoma cell line COLO-206F (DSMZ Accession No. ACC 2 I), the HT-29 human colorectal adenocarcinoma cell line (ATCC Accession No. HTB-38), ASPC-1 pancreatic carcinoma cells, and BXPC-3 pancreatic carcinoma cell line, see p. 55.

The specification teaches that PM-2 induces apoptosis in BXPC-3 human pancreatic carcinoma cells after 24 hours of incubation, see Example 4, and Fig. 4A and 4B, 7 and 9. Additionally, the specification teaches that PM-2 inhibits the viability and proliferation of human pancreatic carcinoma BXPC-3 cells, see Example 5 and Fig. 3 and 8.

The teachings of the specification cannot be extrapolated to enable the scope of the claims because the claims encompass epitopes and proteins that would not predictably be bound by the PM-2 antibody or antibodies comprising SEQ ID NO: 5 and 7 or variants thereof, i.e. antibodies that bind to a polypeptide or an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) that are distinct from the epitope or polypeptide bound by PM-2 because the exquisite sensitivity of binding proteins to alterations of even a single amino acid is well known in the art. For example, Coleman et al. (Research in Immunology, 1994; 145(1): 33-36, previously cited) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Furthermore, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, see abstract in particular) teach single amino acid substitutions outside the antigenic site on a protein affects antibody binding. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by

Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore Pero et al. (US PG Pub 2003/0105000) specifically teach that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50% similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2, see para 0255 of the published application. These references demonstrate that even a single amino acid alteration or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein. Thus, given that the claims encompass PM-2 antibodies and variants thereof to bind to unknown epitopes on unknown proteins and given the unpredictability of the PM-2 antibody interacting with distinct epitopes on distinct proteins, undue experimentation would be required to make and use the antibody as broadly claimed.

Additionally, one of skill in the art cannot extrapolate the teachings of the specification to the scope of the claim because the claims encompass a genus of antibodies binding a genus of epitopes on a genus of undefined proteins and one of skill in the art cannot predictably expect that this genus of antibodies will induce apoptosis in BXPC3 cells, inhibit proliferation of BXPC3 cells or pancreatic adenocarcinoma cells, or bind to other cancer cell types by targeting the broad genus of epitopes because the ability of an antibody to bind an epitope or antigen is not predictive of other antibody activities towards the cells and the expression a polypeptide by BXPC-3 or ASPC-1 cells is not predictably indicative of the protein's expression by pancreatic adenocarcinoma or other cancers in vivo because of the expression of proteins in cultured cell lines is not predictably indicative of the proteins expression *in vivo* because of the artifacts associated with cultured cells *in vitro* and the heterogeneity of cancer is well known in the art .

As drawn to the correlation between antibody binding to an epitope and other activities of the antibody, Young et al. (US Pat. App. Pub 2004/0258693, Dec. 23, 2004) teach that the monoclonal antibody 7BD-33-11A binds to multiple cell lines, but only induced cytotoxicity in a small subset of those cells to which it bound, see Table 1 and 2 and para. 0100-0102. Additionally, Young et al. (US Patent Application Pub. 2004/0197328, October 7, 2004) teaches that monoclonal antibody 11BD-2E11-2, which is cytotoxic towards some cell lines, binds to MDA-MB-231 cells, but is not cytotoxic towards them, see para 0100-0104 and Tables 2 and 3. Furthermore, Young et al. (US Patent Application Pub. 2004/0197328, October 7, 2004) teach that while monoclonal antibody 11BD-2E11-2, which recognizes Melanoma-associated chondroitin sulfate proteoglycan (MCSP), is effective for treatment of breast and ovarian tumors (see examples 7 and 8), other monoclonal antibodies that also recognize MCSP, such as 9.2.27 and 225.28S, were generally ineffective as therapeutic antibodies, see para. 0014-0019. Thus even for monoclonal antibodies that recognize the same protein or epitope, it cannot be predicted if the antibody will have the same activity towards different cells expressing the targeted protein or epitope. Furthermore, it is not clear from the teachings of the specification or the art of record if it is the binding of PM-2 to the 115 kDa protein, the 55 kDa protein (see Fig. 5) or an approximately 80 kDa protein with similarity to the integrin binding protein p80 or the protein REV1 (see US Pat. App. Pub. 2008/0281083 (Vollmers et al. Nov. 13, 2008) Abstract and Fig. 3) that is responsible for the activities of the PM-2 antibody in regard to cell proliferation and

apoptosis. Thus, given the breadth of the claimed antibodies that bind to a genus of epitopes on a genus of proteins and the unpredictability of correlating the activities of an antibody with its binding to an epitope or protein and given that only the PM-2 antibody that binds the 115 kDa protein expressed by ASPC-1 and BXPC-3 has been shown to induced apoptosis or inhibit proliferation in a single pancreatic cell line, undue experimentation would be required to make an use the invention as broadly claimed.

As drawn to the artifactual nature of cell lines, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor as set forth above. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4, previously cited), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12: 320, previously cited) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25, previously cited) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802, previously cited) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Thus, given that claims encompass antibodies that bind unknown epitopes on unknown polypeptides distinct from that bound by PM-2, the expression of these unknown proteins by BXPC-3 or ASPC-3 would not predictably be indicative of the proteins expression in pancreatic carcinoma or other carcinomas *in vivo*.

Additionally, as drawn to cancer heterogeneity, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274, previously

cited). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between PM-2 and inhibition of pancreatic cell growth, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850, previously cited), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729, previously cited) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between the binding of PM-2 to the two pancreatic cell lines and ASPC-1 and BXPC-3 and the binding of the broadly claimed antibodies, which are not limited to binding the polypeptide bound by PM-2, to the multiple tumor types claimed based on the information in the specification and known in the art without undue experimentation. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicants argue that the rejection due to the claims allegedly encompassing "a genus of antibodies binding to a genus of unknown epitopes on unknown proteins," the claims are directed to antibodies and antigen binding fragments that specifically bind to the epitope that the PM-2 antibody specifically binds. Accordingly, the claimed antibodies and antigen binding fragments bind to the epitope that the PM-2 antibody binds the claimed antibodies bind to a single epitope, and do not bind to a "a genus of epitopes." Consequently, the alleged basis for rejection due to

the antibodies and fragments allegedly binding to a genus of epitopes (e.g., pages 7, 9 and 10, and the cited Coleman, Abaza et al. and Burgess et al. references) is inapplicable to the claims.

Applicants argue that in terms of the rejection based upon the Pero et al. publication (US 2003/0105000) cited at page 9 of the Action, this reference describes differences in binding of SH2 containing Grbl4 proteins to another protein (ErbB2) and peptide-phage sequences, not binding between antibodies and antigens. Thus, Pero et al. describes interactions between other proteins that are unrelated to antibody-antigen interactions. Furthermore, as discussed above Applicants' claims are not directed to variant antigen sequences in the sense that the antibodies and antigen binding fragments bind to different antigens having different epitopes. Consequently, the Pero et al. publication (US 2003/0105000) is irrelevant to whether or not the claimed antibodies and antigen binding fragments are adequately enabled under 35 U.S.C. § 112, first paragraph.

Applicants argue that in terms of the rejection at page 10 and pages 11-14 of the Action allegedly due to "one of skill in the art cannot predictably expect that this genus of antibodies will .... bind to other cancer cell types" or that "expression of proteins in cultured cell lines is not predictably indicative of the proteins expression in vivo because of artifacts associated with cultured cells in vitro, and the heterogeneity of cancer," Applicants need not enable what is not claimed and claims 111 to 116, 120 to 125, 127 to 130 and 134 recite binding to at least one of two well defined cell lines, namely ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687). Thus, because claims 111 to 116, 120 to 125, 127 to 130 and 134 do not require that the antibodies "bind to other cancer cell types" or bind to various cancer

cells in vivo this ground for rejection is irrelevant to enablement of claims 111 to 116, 120 to 125, 127 to 130 and 134.

Applicants argue that in terms of claim 126, which recites that the claimed antibodies or antigen binding fragments bind to certain adenocarcinomas or carcinomas, one of skill in the art could readily identify antibodies and antigen binding fragments that bind to the adenocarcinomas or carcinomas, without undue experimentation. In this regard, the specification discloses methods for assaying antibody binding using IHC staining of cryosections of human tumors (page 46, line 25, to page 47, line 10). The specification discloses that using this assay revealed that PM-2 reacted with a large number of carcinomas and adenocarcinomas (page 53, lines 22-25, and page 54, Table 4). Thus, in view of the guidance in the specification which discloses a routine screen to determine antibody binding one of skill in the art could readily identify antibodies and antigen binding fragments that bind to any of the recited adenocarcinomas and carcinomas in claim 126 without undue experimentation.

Applicants argue that in terms of the ground for rejection at the paragraph bridging pages 10 and 11 of the Action allegedly due to antibodies being cytotoxic towards some cell lines but not others, Applicants need not enable what is not claimed and claims 111 to 116, 120 to 126, 130 and 134 do not require cell cytotoxicity. Thus, the grounds for rejection due to absence of cytotoxicity against a given cell line is irrelevant to enablement of claims 111 to 116, 120 to 126, 130 and 134.

Applicants argue that in terms of claims 127 to 129, which recite that the claimed antibodies or antigen binding fragments "inhibit proliferation" or "induce apoptosis" of BXPC-3 or adenocarcinoma cells of the pancreas, one of skill in the art could readily identify antibodies

and antigen binding fragments that inhibit proliferation or induce apoptosis of BXPC-3 or adenocarcinoma cells of the pancreas without undue experimentation. In this regard, the specification discloses methods for ascertaining antibody induction of apoptosis and inhibition of cell proliferation (Examples 4 and 5, respectively). The specification discloses that these assays revealed that PM-2 induced apoptosis and inhibited cell proliferation of BXPC-3 cell line (page 56, lines 8-29, and page 57, line 28, to page 58, line 30). Thus, one of skill in the art, in view of the guidance in the specification could readily identify any antibody or antigen binding fragment in claims 127 to 129 that inhibits proliferation or induces apoptosis using a routine screen and without undue experimentation.

Applicants argue that the proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731,737 (Fed. Cir. 1988). Applicants argue that in view of the guidance in the specification and knowledge and skill in the art at the time of the invention variants of antibodies and antigen binding fragments having the requisite activity could be made and used without undue experimentation using routine methods disclosed in the specification or that were known in the art at the time of the invention.

Applicants argue that here, amended claims 111 to 116, 120 to 130 and 134 are analogous to Wands, where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue

experimentation. Likewise, undue experimentation would not be required to make and identify variant antibodies and antigen binding fragments that bind to an epitope of a polypeptide expressed by at least one of the recited cell lines, to which epitope PM-2 antibody binds, given that 1) producing antibody variants and fragments was routine in the art at the time of the invention; and 2) binding assays are disclosed in the specification and other antibody binding assays were known in the art at the time of the invention. Thus, there is no need for the skilled artisan to "predict" antibody variants or binding fragments that bind to the epitope of the polypeptide to which PM- 2 antibody binds because making antibodies and fragments and identifying those that bind was routine in view of the guidance in the specification and knowledge in the art at the time of the invention.

Applicants argue that consequently, the statements in the Office Action (e.g., pages 10, 11, 13 and 14) that purportedly support the rejection, namely that allegedly one of skill in the art "cannot predictably expect that the genus of antibodies will induce apoptosis of BXPC-3 cells or pancreatic adenocarcinoma cells" or allegedly "the unpredictability of correlating the activities of an antibody with its binding to an epitope or protein" or that allegedly "no evidence has been provided which would allow one of skill in the all to predict that the invention will function as contemplated or claimed," are irrelevant to enablement of the claims since there is no need to predict the effect of any amino acid change in order to make and identify antibodies and antigen binding fragments having the recited activities without undue experimentation.

Applicants argue that in support of Applicants position, claims directed to a genus of antibodies where no antibody has ever been produced are routinely granted by the Patent Office. Thus, if claims covering a genus of antibodies have been granted where no antibody has even

been made and therefore where no antibody sequences are even known, surely knowledge of antibody sequence or predicting the effects of particular amino acid variations on binding is not required to satisfy the enablement requirement under 35 U.S.C. § 112. Consequently, it is clear that enablement of the claims under 35 U.S.C. § 112 does not require knowledge of antibody sequence or predicting the effects of particular sequence variations on antibody binding. Thus, the repeated statements by the Patent Office that one would have to predict the effect of changes in antibody sequence clearly indicates that the Patent Office is applying an incorrect standard for enablement of the claims.

Applicants argue that that the Patent Office cannot insist that the specification enable the claims by a particular methodology, namely predicting in advance which antibody variants would bind or have another activity. In this regard, there is no authority requiring Applicant to demonstrate enablement by a particular methodology selected by the Patent Office, to the exclusion of other methodologies. Consequently, for the Patent Office to demand that Applicant demonstrate enablement by a particular methodology under 35 U.S.C. § 112, first paragraph, is clearly improper under 35 U.S.C. § 112.

Applicants argue that the level of knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Methods of producing antibody fragments (e.g., Fv, Fab, Fab' and F(ab')2) were known in the art and were routine at the time of the invention. Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of

the invention, one skilled in the art could readily make antibodies and antigen binding fragments without undue experimentation.

Applicants argue that second, methods of identifying antibodies and fragments that bind antigen without undue experimentation are also taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 14, lines 9-27; page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Thus, antibodies and binding fragments that bind to an epitope of a polypeptide expressed by at least one of ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687) cells, to which epitope PM-2 antibody produced by a cell line deposited as DSM ACC 266 binds, as well as antibodies and antigen binding fragments that inhibit cell proliferation and induce apoptosis, could be identified without undue experimentation at the time of the invention.

Applicants argue that for example, if one skilled in the art wanted to produce antibodies or antigen binding fragments that specifically bind to an epitope of a polypeptide expressed by at least one of ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL- 1687) cells, to which epitope PM-2 antibody produced by a cell line deposited as DSM ACC 2600 also binds, the skilled artisan could simply introduce mutations in a light and/or heavy chain variable region sequence (SEQ ID NOs: 5or 7) and then verify those that bind to the epitope to which PM-2 binds, for example, by a competition binding assay with PM-2 antibody for binding to ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells. A particular example of the routine nature of methods of producing and

identifying variant antibodies having binding activity at the time of the invention is submitted herewith as Exhibit E (Boder et al., Proc. Nat'l Acad. Sci. USA 97:10701 (2000)). The authors of Exhibit E describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Notably, the authors state "[t]he relative ease with which extremely high affinity has been attained in this study." (page 10705, first column, last full paragraph) Consequently, in view of the fact that functional variants with improved affinity could be made "with relative ease" at the time of the invention, one of skill in the art clearly would have been able to produce variant antibodies and fragments having binding affinity without any need to predict in advance the effect of any amino acid variation without undue experimentation at the time of the invention.

Applicants argue that in sum, analogous to *In re Wands* where the court held that identifying hybridomas that have a particular binding characteristic did not require undue experimentation, making and identifying the claimed antibodies and antigen binding fragments would not require undue experimentation, given that 1) producing antibodies and fragments was routine in the art at the time of the invention; and 2) routine cell binding, antibody competition and cell proliferation/apoptosis assays are disclosed in the specification or were known in the art at the time of the invention. Consequently, contrary to the statements in the Office Action where it is believed that one skilled in the art would have to "predict in advance" the effect of sequence changes on binding, there is no need for the skilled artisan to "predict" variants or fragments that bind to the recited polypeptide in order to make variants and antigen binding fragments because making and identifying antibodies and antigen binding fragments was routine at the time of the invention.

Applicants argue that thus, in view of the high level of knowledge and skill in the art at the time of the invention clearly the skilled artisan could make antibodies and fragments and identify those that bind in view of the guidance in the specification and knowledge in the art at the time of the invention without undue experimentation. Consequently, amended the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn

Applicants' arguments have been considered, but have not been found persuasive. Unlike the situation, *In re Wands,* the claims encompass producing a specific sub-genus of antibodies that retain specific binding to the epitope bound by the PM-2 antibody. In particular, the claims encompass antibodies or fragments thereof with only fragments or percentages of SEQ ID NO: 5 or SEQ ID NO: 7 in the antibody which encompass antibodies missing all or a portion of the CDRs of SEQ ID NO: 5 or 7. Thus, although antibodies could be identified that bound to the epitope bound by the PM-2 antibody by methods such as those described by Boder et al., the claims encompass antibodies that contain deletion or mutation of or one or all of the CDRs of SEQ ID NO: 5 or SEQ ID NO: 7 and given the importance of these regions to the specific binding to an epitope and given the unpredictability of mutating these regions and retaining specific binding to an epitope, one of skill in the art could not make and use the invention as broadly claimed without undue experimentation. Furthermore, the Office is not requiring Applicants to use a particular methodology for making the claimed antibody, rather the Office is stating that undue experimentation is required based on the factors outlined in *In re Wands* and set forth in MPEP 2164.01, given the teaching of the specification and the level of skill in the art at the time the invention was made. Thus, although the level of skill in the art was high at the time the invention was made, the specification has not provide sufficient guidance to satisfy the

enablement requirement to make the broadly claimed antibodies that retain specific binding to an epitope bound by the PM-2 antibody on a 115 kDA protein expressed by the ASPC-1 or BXPC-3 cell lines with the mutations of SEQ ID NO: 5 or 7 encompassed by the claims. Additionally, the specification has only shown that the PM-2 antibody inhibits proliferation in the BXPC-3 cell line and given that even for antibodies that recognize the same protein or epitope it cannot be predicted if the antibody will have the same activity towards another cells expressing the targeted protein or epitope, one of skill in the art could not make and used the antibodies as broadly claimed to inhibit the proliferation of any adenocarcinoma cells of the pancreas with out undue experimentation.

Applicants argue that in addition to the fact that one skilled in the art could make and identify antibodies and fragments at the time of the invention without undue experimentation, the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, as discussed at length in the Office Action the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding was well understood by the skilled artisan at the time of the invention. Applicants argue that the specification also discloses the role of heavy and light chain variable regions, including CDRs, in binding activity (page 22, line 6, to page 23, line 2), and the predicted location and sequences of all CDRs in SEQ ID NOs: 5and 7 (see, e.g., Figures 14 and 15; page 5, lines 7-8; and page 50, lines 14-19). In view of the fact that the predicted locations of all 6 CDRs are taught by the specification, the skilled artisan would also know the locations of all FRs in SEQ ID NOs: 5 and 7.

Applicants argue that in view of the high level of knowledge and skill in the art at the time of the invention and the guidance in the specification clearly the skilled artisan would be apprised of antibody regions and amino acid sequences that participate in binding. Thus, one of skill in the art would have known regions of SEQ ID NOs: 5 and 7 more or less amenable to substitution. Consequently, even if for the sake of argument the skilled artisan wanted to choose particular amino acid residues to vary, even though such *a priori* selection is not required in order to make the claimed antibodies and fragments without undue experimentation, nor is such selection required to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, in view of the extensive knowledge in the art the skilled artisan could indeed select variants with a high probability of having at least partial binding activity.

Applicants argue that to further corroborate that one of skill in the art could produce antibodies and fragments having at least some detectable binding affinity, inhibit cell proliferation or induce apoptosis without undue experimentation at the time of the invention, submitted herewith is a Declaration under 37 C.F.R. §1.132, executed by Dr. Peter Vollmers. As stated in the Declaration, Dr. Vollmers, based upon objective facts and conclusions based upon the objective facts, concludes that one of skill in the art, in view of the guidance in the specification and knowledge in the art at the time of the invention, could produce antibodies and functional fragments having binding activity without undue experimentation (Paragraph 20). The facts and Dr. Vollmers' conclusions based upon the facts are summarized in the Declaration, Paragraphs 20-24. Accordingly, the Declaration under 37C.F.R. § 1.132, executed by Dr. Peter Vollmers corroborates that one of skill in the art could produce variant antibodies and functional

fragments having binding affinity, inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

Applicants argue that in sum, given the fact that one skilled in the art could make and identify variant antibodies and functional fragments that bind to an epitope of a polypeptide expressed by at least one ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells to which PM-2 antibody produced by a cell line deposited as DSM ACC 2600 also binds without undue experimentation at the time of the invention, there is no need to predict the effect of variations on antibody binding. In addition, the Patent Office cannot properly demand that Applicants demonstrate enablement of the claims by a particular methodology to satisfy 35 U.S.C. § 112, lust paragraph, i.e., be able to predict variants. Here, one skilled in the art is not required to predict the effect of any change in order to make and identify antibodies and fragments that bind, inhibit proliferation or induce apoptosis without undue experimentation, as held by the court in Wands, and corroborated by Exhibit A and the Declaration under 37C.F.R. § 1.132, executed by Dr. Peter Vollmers. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of the rejection.

Applicants' arguments have been considered, but have not been found persuasive. Although antibodies could be identified that bound to the epitope bound by the PM-2antibody by methods such as those described by Boder et al. or Dr. Peter Vollmers, the claims encompass a specific sub-genus of antibodies that contain deletion or mutation of or one or all of the CDRs of SEQ ID NO: 5 or SEQ ID NO: 7 and given the importance of these regions to the specific binding to an epitope and given the unpredictability of mutating these regions and retaining

specific binding to an epitope, one of skill in the art could not make and use the invention as broadly claimed. Furthermore, the Office is not requiring Applicants to use a particular methodology for making the claimed antibody, rather the Office is stating that undue experimentation is required based on the factors outlined in *In re Wands* and set forth in MPEP 2164.01, given the teaching of the specification and the level of skill in the art at the time the invention was made. Thus, although the level of skill in the art was high at the time the invention was made, the specification has not provide sufficient guidance to satisfy the enablement requirement to make the broadly claimed antibodies that retain specific binding to an epitope bound by the PM-2 antibody on the 115 kDA protein expressed by the ASPC-1 or BXPC-3 cell lines. Additionally, the specification has only shown that the PM-2 antibody inhibits proliferation in the BXPC-3 cell line and given, as previously set forth, that even for antibodies that recognize the same protein or epitope, it cannot be predicted if the antibody will have the same activity towards cells expressing the targeted protein or epitope, one of skill in the art could not make and use the antibodies as broadly claimed for inhibition of pancreatic adenocarcinoma cell growth without undue experimentation for the reasons previously set forth and above.

It is noted that claims 121 and 122 would be allowable if re-written as independent claims and the wherein clauses were amended to recite that the antibody, as well as the antigen binding fragment, comprises the recited CDR sequences of SEQ ID NO: 5 and/or 7.

5. All other objections and rejections recited in the Office Action of 07/31/2009 are withdrawn.

6. Claims 111-116, 120-122, and 124-130 are rejected.

7. Claim 123 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Claims 133 and 134 appear allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642